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Endophenotype Strategies for the Study of Neuropsychiatric Disorders

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Consortium for the Human Information and Neurocognitive Endophenotype (CHINE) in mainland China: An example from neurological soft signs for neuropsychiatric disorders

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Increasing efforts to identify alternate expressions of neuropsychiatric disorders that are broader than the DSM or ICD diagnostic criteria needed to diagnose them reflects a growing consensus that multidimensional expressions of neuropsychiatric disorders may advance the search for underlying etiological or modulatory factors. Endophenotypic research can be considered to be one of the most promising strategies to bridge the gap between genomic complexity and the phenotypic heterogeneity observed in neuropsychiatric disorders. However, the majority of endophenotype studies were limited to our western counterparts, very little has been done and initiated by scholars in mainland China. In this paper, we urge the need to establish a potential central consortium for endophenotypes to study neuropsychiatric disorders in mainland China. In particular, we illustrate a potential example of neurological soft signs in following the steps for building the consortium.

endophenotypes, neurological soft signs, neuropsychiatric disorders, mental health, China

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This strategic paper argues the need for establishing a central consortium for the endophenotype approach for neuropsychiatric disorders in mainland China. We start with a brief introduction to endophenotypes, what is known about the concept of endophenotypes, and then to illustrate the claim that endophenotypes are more important than traditional genetic approach of studying neuropsychiatric disorders. This is not our intention to provide a comprehensive review of all endophenotypes employed in neuropsychiatric disorders in this strategic paper because there are several systematic reviews on this aspect [1–4]. However, we would illustrate an example of a promising endophenotype, neurological soft signs, in detailing the steps for building the consortium.

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1 The concept of endophenotype

The term "endophenotype" was firstly coined by John and Lewis [5] who used it to explain concepts in evolution and inset biology. The Greek word "endos" means interior and within. By that time, John and Lewis attributed the geographical distribution of grasshoppers was a function of some feature not apparent in their "exophenotypes", and this feature was "the endophenotype, not the obvious and external but the microscopic and internal". Gottesman and Shields [6,7] then adapted this term to specifically link glucose tolerance test as an endophenotype that are heritable biomarkers not observed by the naked eye. According to this new definition, Gottesman and Shields intended to link this glucose tolerance test as an endophenotype for diabetes. The term, endophenotype, however, is also very useful to suit the needs of psychiatric genetics, and to fill the gap

between available descriptors and between the gene and the elusive disease processes. Endophenotypes in psychiatry nowadays retain the notion of an internal process that cannot be observed with naked eyes but can be objectively and reliably measured.

Despite the inherent advantages and innovation of the concept postulated by Gottesman and Shields, endophenotypes have been received relatively attention as compared to genetic approach. However, as more and more evidence coming from genetic studies have proven unsuccessful, the merits of endophenotypes outstanding the conventional genetic approach in neuropsychiatric disorders research more clearly [6,7]. First, the uncertain and phenomenological nature of psychiatric diagnosis makes reference to a biological level of description attractive. Second, the complexity of the human brain obviously necessitates an effort to parse this problem into tractable biological subprocesses [2].

2 Advantages of endophenotypes strategy for neuropsychiatric disorders research

Despite the fact that genetic contributions to complex neuropsychiatric disorders such as schizophrenia and bipolar disorders are well-accepted [8–10], the identity of most genes that increase susceptibility to the disorders, and the biological mechanism by which they act, are still largely unknown. The completion of human genome sequencing does not mean we can grasp a more comprehensive view about the etiologies of these complicated neuropsychiatric disorders since the study of these disorders is complicated by the polymorphisms of the diseases, impact of environment as well as interaction between genes and environment [11,12]. Conventional genetic approach has shown an unsuccessful outcome evidenced by the unreplicated findings and unrealized expectations. Given that endophenotypes represent more defined and quantifiable measures that are envisioned to involve fewer genes, fewer interacting levels and ultimately activation of a single set of neuronal circuits, they are potentially more tractable to genetic dissection than the mental disease states [2]. It provides a very good alternative method to study the etiologies of complex polymorphism neuropsychiatric disorders.

The application of endophenotype approach reserves a number of merits to study neuropsychiatric disorders as compared to the conventional genetic approach such as the neural-based endophenotypes may more directly reflect the activities of synaptic and other neuronal mechanisms than does the more complex illness itself; the endophenotypes can also be investigated via brain-imaging and infrahuman animal model research [1,4,13]. Moreover, many risk gene associations to brain-based phenotypes can also be observed in healthy individuals suggesting that this approach offers a very powerful bottom-up strategy to discover biologically valid knowledge about previously unknown mechanisms [14].

3 Criteria and clinical steps for endophenotypes research

There are several stringent criteria to be fulfilled for being an endophenotype for a particular neuropsychiatric disorder such as schizophrenia and bipolar disorders. To name briefly, these are association with the illness, be heritable, be primarily state independent, and co-segregate within families and can be reliably measured [1,2,15]. Recently, the Consortium on the Genetics of Schizophrenia (COGS) funded by the National Institute of Mental Health (NIMH) has refined and extended the criteria for endophenotypes [4,16, 17]. The selection of the neurocognitive measures for COGS is listed below:

(1) Association with illness is specifically referring to moderate to large effect sizes between schizophrenia patients and community controls.

(2) State independent is further divided into detailed psychometric properties of the measure itself over a period of time (adequate test-retest stability) and reliability between among different sites (adequate between-site reliability). Moreover, strong evidence has to be gained for the observed impairments in patients are not due to medications, including direct comparisons between medicated vs. unmedicated patients, medication-naive vs. medicated patients, and correlations between performance and medications; evidence that impairments are observed regardless of the illness state, including that first-episode, chronic, and remitted patients exhibit similar patterns of impairments.

(3) Heritability of the endophenotypes is further divided into the heritability in healthy populations and in schizophrenia families.

(4) Found in unaffected relatives at a higher rate than in the general population so that small to moderate effect sizes between biological relatives of schizophrenia patients and community controls are observed.

(5) The elected measures should have a known neurobiological substrate relevant to schizophrenia and whose initial results support using them to test genetic hypotheses.

(6) The practicality of task administration in a large multisite protocol.

Braff et al. [13] further delineate a systematic procedure for researchers to adopt the endophenotype strategy for neuropsychiatric disorders research. These are (1) clinical observation that gives rise to the prevalence of specific indicators in the clinical group as compared to healthy controls; (2) quantifiable measurement based on laboratory findings or related neuropsychological tests to demonstrate the magnitude of deficits; (3) heritability and genetic studies to identify any familial-transmitted traits; (4) modeling of

brain imaging to clarify the neural basis of the trait, and specific molecular variations identified from family and association studies; and (5) drug development as the ultimate outcome.

4 The Consortium on Human Information and Neurocognitive Endophenotypes (CHINE)

Here we argue the need to set up a nation-wide database for neuropsychiatric disorders, namely the Consortium on Human Information and Neurocognitive Endophenotypes (CHINE) [18]. The CHINE is intentionally established to follow the roadmap of the NIMH on the identification of the biosignatures for neuropsychiatric disorders and to serve as the central databank for examining the etiologies of major complex neuropsychiatric disorders as well as serving the main basis for corresponding treatment development. The CHINE emphasizes on two main features, i.e., the supposedly universal basic cognitive functioning such as attention, and the supposedly culturally specific social cognitive functioning such as emotion perception and expression. In this consortium, we are going to collect data at three main levels highlighting the genetic level (susceptibility genes associating with major neuropsychiatric disorders such as schizophrenia, bipolar disorders, ADHD etc.), neuroanatomical level (structural and functional imaging data), behavioural level (neurocognitive function performances, social cognitive functioning, neurological and clinical manifestations). Target groups include both the clinically diagnosed patients suffering from neuropsychiatric disorders (mainly schizophrenia and bipolar disorders at the current moment, but will be extended to other clinical groups later), non-psychotic first-degree relatives of the patients, and healthy controls.

Here we would like to illustrate the structure of this consortium with an example from neurological soft signs. Chan and Gottesman [19] have systematically provided substantial evidence to support the candidature of neurological soft signs as potential endophenotypes for schizophrenia [2,6,13]. Figure 1 illustrates the neurological soft signs and other related neurocognitive functions are the crucial indicators to bridge the gap between the microscopic level of genomics and brain structures and the macroscopic level of clinical manifestations in understanding the etiology of schizophrenia.

Figure 2 illustrates how neurological soft signs database fits into the logic of these steps. It should be noted that the final step for drug development will take quite a lot of time to be achieved. We will base our opinion on this database we have established in China and the existing literature from western studies to illustrate such a claim.

5 Illustration of neurological soft signs as an example from CHINE

(i) Step 1: Clinical observation. The prevalence rate of neurological signs among patients with schizophrenia ranges from 50% to 65% in contrast to 5% in healthy controls in western samples [20,21]. However, specifically for soft signs, the prevalence rate ranges from 9% to 82% as compared to 3% to 12.5% [22–29]. The only available data for Chinese patients with schizophrenia and healthy controls reveals that the prevalence rates in Chinese patients with schizophrenia and healthy controls are 59% and less than 5%, respectively [30].

Our Chinese database indicates the prevalence rate of soft signs in unaffected first-degree relatives of schizophrenia ranges from 5% to 66% [31]. The meta-analysis from our

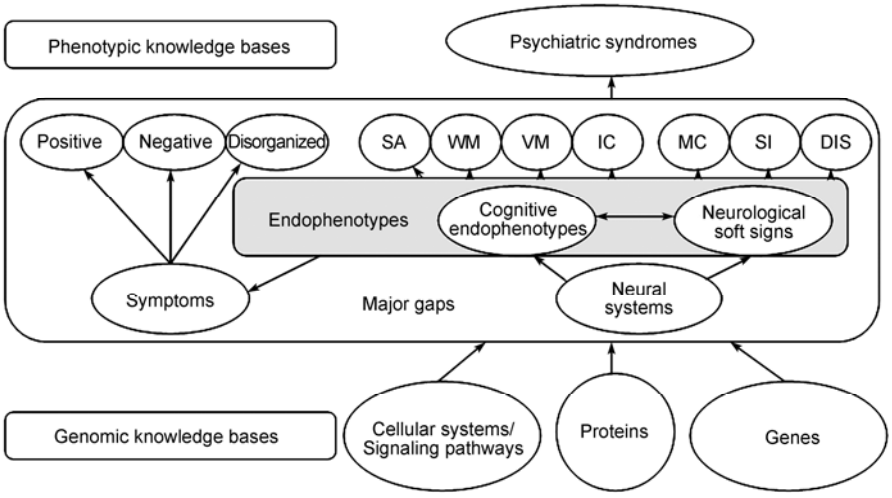

Figure 1 Endophenotypes serve as the intermediate layer to bridge the gap between phenotypic and genomic knowledge bases of schizophrenia. Cognitive phenotypes: SA, sustained attention; WM, working memory; VM, verbal memory; IC, inhibitory control. Neurological soft signs: MC, motor coordination; SI, sensory integration; DIS, disinhibition.

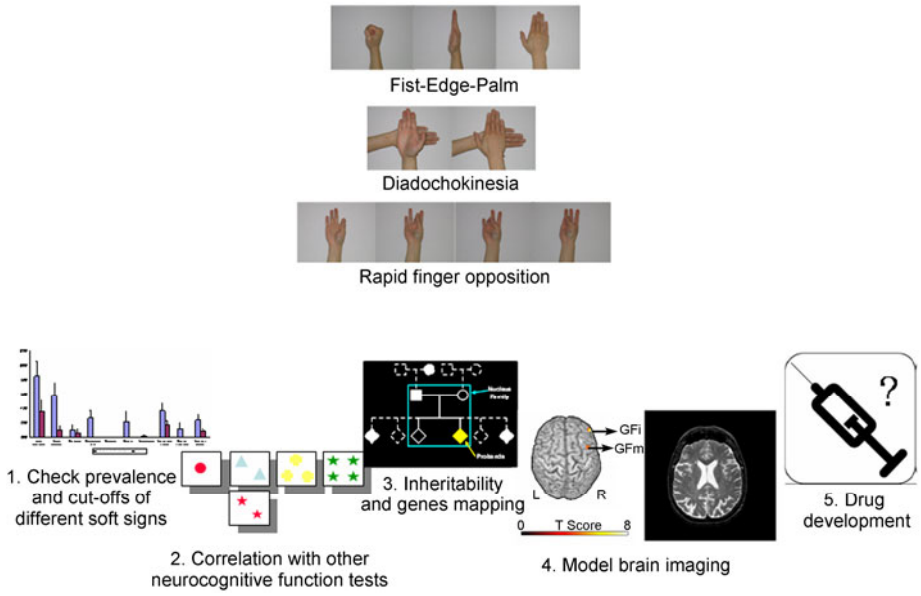

Figure 2 Five steps of endophenotype strategy for building up the neurological soft signs database in schizophrenia.

laboratory suggests that the effect size of the prevalence for nonpsychotic siblings of patients with schizophrenia compared to their affected siblings and healthy controls was 0.75 and 0.95, respectively [32]. Another meta-analysis [33] also shows that there are large effect sizes of deficits (Cohen's *d*) found in patients with chronic schizophrenia and first-episode schizophrenia contrasted with normal controls. The effect sizes of motor coordination signs, sensory integration signs, and complex motor sequencing signs in chronic patients are 0.86, 0.88, 0.80, respectively, whereas those for the first-episode patients are 1.020, 0.84, and 0.78, respectively. Specifically to the Chinese samples, the effect sizes of motor coordination signs, sensory integration signs, and disinhibition signs in chronic patients are 0.94, 0.56, and 0.99, respectively. Moreover, similar deficits of neurological soft signs have also been found in nonpsychotic family members of schizophrenia, with the magnitudes of deficits intermediate between patients and healthy controls. The effect sizes of motor coordination, sensory integration and complex motor sequencing between patients and nonpsychotic family members are 0.83, 0.34, and 0.61, respectively, whereas those between nonpsychotic family members and healthy controls are 0.31, 0.32, and 0.14, respectively [32].

(ii) Step 2: Quantifiable measurement. The standardization of a measuring tool is the essential step to proof for its reliability and validity in measuring the construct we are intending to do. Although neurological soft signs were conventionally considered to be the signs induced by non-localizing brain regions, most recent findings demonstrate that these signs can be measured reliably and validly [34,35]. Moreover, some also suggest there will be a localized specific pathway or connection instead of a diffused brain regions involvement (c.f. modeling of organism and brain imaging section below). Our database also suggests that, at the conceptual and construct levels, neurological soft signs are more or less capturing the same construct measured by traditional neurocognitive tests using the structural equation modeling approach [36]. All the neurological soft signs subscales such as motor coordination, sensory integration, and disinhibition were significantly correlated with executive function, verbal memory, and visual memory. The same model were demonstrated in two independent samples of schizophrenia and healthy volunteers, suggesting that neurological soft signs and conventional neurocognitive functioning tests are capturing the same underlying deficits of brain functions in schizophrenia.

(iii) Step 3: Heritability and genetic mapping. Existing literature from the western sample suggest that portion of the neurological soft signs, particularly the motor coordination and complex motor sequencing tasks are highly heritable, e.g., rapid alternating movement (h^2 0.99±0.19 for completion time), go-nogo task (h^2 0.93±0.33 for correct responses), alternating fist-palm test (h^2 0.77±0.19 for completion time; h^2 0.7±0.32 for errors), and fist-ring test (h^2 0.53±0.23 for right-sided completion time; h^2 0.7±0.21 for left-sided completion time). However, Braff et al. [13] emphasize that the endophenotype strategy is to find out not only a heritable trait or marker but also a "mappable" one linking to genetic basis. They have illustrated this point with their COGS project by referring the mappability of P50 suppression to SNPs in the promoter region of the alpha-7 nicotinic receptor [37] and its potential development and initial clinical trials of alpha-7 nicotinic agonists for the treatment of schizophrenia [38].

For neurological soft signs, twins data from limited western samples suggest that schizophrenia and neurological

soft signs share genetic influences but indicate that the genetic overlap between schizophrenia and neurological soft signs is not very substantial [39–41]. However, these findings might have been limited by the small number of twin studies and the corresponding small sample sizes. Our preliminary findings from a total of 250 healthy twins data suggest that the heritability of motor coordination, sensory integration, disinhibition subscores, and the total score of neurological soft signs is 0.67, 0.41, 0.41, and 0.75 respectively. However, more data from Chinese familial design and clinical twins are needed to further confirm the specific heritability of neurological soft signs in schizophrenia. With the significant levels of heritability of neurological soft signs, at least in motor coordination, we have strong reason to believe that mappability and gene discovery will be a feasible step to be accomplished in the near future.

(iv) Step 4: Modelling of organism and brain imaging. In order to provide a stronger neural basis of neurological soft signs in schizophrenia, our strategy is to leverage these signs to conventional neurocognitive functions, the related brain structures and connectivity. We hope that we can map these signs to genes identified as responsible for aberrant brain mechanisms in this clinical group. However, the underlying cerebral changes have not yet been fully identified. Limited structural brain imaging from western samples suggest that neurological soft signs are associated with enlargement of cerebral ventricles [42], smaller brain areas [43], particularly in grey matter involving in sub-cortical regions such as putamen, globus pallidus and thalamus as well as cerebellum [44–48]. A similar reduction in grey matter volumes in these regions was also demonstrated in healthy volunteers [49]. However, a most recent study done by Thomann et al. [47] found grey and white matter density of distinct brain regions to be significantly associated with severity of neurological soft signs in 42 patients with first-episode schizophrenia but not healthy controls. In particular, the regions involved the pre- and post-central gyrus, premotor areas, inferior and middle frontal gyri, caudate nucleus, thalamus, and cerebellum.

Three functional imaging studies found neurological soft signs to be associated with sensorimotor cortex changes [50–52]. Günther et al. [53] found a bilateral overactivation in the precentral gyrus in Type I patients with schizophrenia and a decreased activation in Type II patients. Schröder et al. [52] demonstrated a decreased activation of sensorimotor cortices and SMA, as well as a reversed lateralization effect in a group of schizophrenia as compared to the healthy controls using the finger-to-thumb opposition task. Heuser et al. [54] further found that there was significantly more variation in pronation/supination motor coordination task in medication naïve schizophrenic patients in addition to a diminished sensorimotor cortex and SMA activation. Taken together, these findings support the model of cognitive dysmetria proposed by Andreasen et al. [55] that strongly suggest the resulting disconnection syndrome underlies both psychopathological symptoms and neurological abnormalities in schizophrenia.

On the other hand, similar associations were found with decreased activation of the sensorimotor cortices and the supplementary motor area using functional neuroimaging techniques [54,56]. Most recently, more sophisticated paradigms using the specific item of motor coordination, namely the Fist-Edge-Palm (FEP), have been developed to examine underlying neural substrates in healthy volunteers. In the FEP task, subject is required to successively place the hand in each of the following postures: a fist resting vertically (i.e., Fist), a palm resting vertically (i.e., Edge), and a palm resting horizontally (i.e., Palm). Umetsu et al. [57] compared right and left hand FEP to relatively simple motor tasks, and revealed FEP-induced activation in the multiple cortical regions including sensorimotor, premotor, parietal, and supplementary motor areas, but not in the prefrontal cortex. Chan et al. [58] also replicated FEP-induced activation in the motor network with no activation in other frontal areas. These results are inconsistent with neuropsychological testing evidence showing that patients with frontal lobe lesions exhibit deficits on the FEP task [59]. A possible explanation may be that frontal lobe in FEP is involved in integration or regulation of neural activities underlying motor sequencing rather than being directly activated by FEP. However, imaging studies using conventional subtraction analyses can only indicate regionally specific effects in the context of functional specialization; therefore have no implication to reveal the potential role of prefrontal regions in the context of functional integration [60]. A re-analysis of these FEP imaging data using psychophysiological interaction (PPI) analysis, however, revealed significantly enhanced functional connectivity between the left and right sensorimotor cortex and the right inferior and middle frontal cortex during the FEP task comparing to a simple motor task [61]. These results support the involvement of frontal lobe function in FEP and suggest a role of motor regulation rather than direct participation of prefrontal cortex in the execution of complex motor sequence task such as FEP neurological soft signs. However, these findings are limited to healthy volunteers and our laboratory is now collecting clinical data to examine the activation pattern and connection in patients with first-episode medication naïve schizophrenia.

(v) A step beyond: A lifespan perspective of neurological soft signs. As noted above these neurological soft signs may not be specific to schizophrenia but also are found in other neuropsychiatric disorders such as ADHD [62–64], and major depression [65], bipolar disorders [66,67]; therefore, the database may be applicable and extended to a wider range of clinical cases with greater public health impact. The lifespan database may facilitate us to calculate the specificity of neurological soft signs in different stages of onset of a specific neuropsychiatric disorder or the corresponding specificity of neurological soft signs in different

clinical neuropsychiatric disorders.

6 Conclusions

Taken together, the specific information from CHINE on neuropsychiatric disorders such as schizophrenia in the context of the Chinese setting at the moment confirm neurological soft signs are promising endophenotypes for schizophrenia. It is equally notable that the demonstrations of neurological soft signs reviewed here represent only a few of the potentially important endophenotypes for schizophrenia in CHINE. Other endophenotypes such as brain abnormalities, neural connectivity, cognitive and social cognitive functioning as well as the clinical data are equally important for the understanding of the neuropsychiatric disorders. The genetic basis of endophenotypes is more tractable to genetic dissection than that of neuropsychiatric disorders. Finally, it is also noteworthy that the potential translational usage of neurological soft signs as a quick, quantifiable, sensitive and user-friendly bedside early detection and screening tool for clinical practice.

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